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PATENT

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7/14/05 Michelle Hodson
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: B. Li
POLO et al.	Group Art Unit: 1648
Serial No.: 09/551,977	Confirmation No.: 2230
Filing Date: April 14, 2000	Customer No.:
Title: COMPOSITIONS AND METHODS FOR GENERATING AN IMMUNE RESPONSE UTILIZING ALPHAVIRUS-BASED VECTOR SYSTEMS	

TRANSMITTAL LETTER

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Appeal Brief (18 pgs) with attached Claims Appendix (2 pgs), Evidence Appendix (12 pgs) and Related Proceedings Appendix (1 pg)

X Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	6	- 37	0	x $50.00	$0
Independent Claims	1	- 9	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Petition for Extension of Time Fee					$0
Appeal Fee					$500.00
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$500.00

x A check in the amount of $500.00.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: July 14, 2005

By: _____
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property – R440
PO Box 8097
Emeryville, CA 94662-8097
Telephone: 650-493-3400
Facsimile: 650-493-3440

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APPEAL BRIEF

ROBINS & PASTERNAK LLP
1731 Embarcadero Road
Suite 230
Palo Alto, CA 94303

Attorney for Appellants

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APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellants submit one copy of their brief on appeal in accordance with Section 41.37 (69 Fed. Reg. 49962, Aug 2004). All claims were finally rejected under 35 U.S.C. § 112 in a Final Office Action dated November 30, 2004. A Notice of Appeal was received May 26, 2005,

making an Appeal Brief due on or before July 26, 2005. Accordingly, this Brief is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

I. REAL PARTY IN INTEREST

Chiron Corporation, the assignee of record of the above-referenced patent application, is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 17 and 19-23 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on April 14, 2000 with claims 1-37. In response to a Restriction Requirement (mailed on May 30, 2001), claims 17 and 19-23 were elected, with traverse. Claims 1-16, 18 and 24-37 were canceled, without prejudice or disclaimer, in an Amendment submitted on January 21, 2003. Claim 17 was amended in papers submitted on March 4, 2002, September 4, 2002, January 21, 2003 and July 25, 2003. Claims 19 and 21-23 were amended in the paper submitted on January 21, 2003. Accordingly, claims 17 and 19-23 are pending as shown in the Claims Appendix. Claim 20 is allowable and claims 17, 19 and 21-23 remain rejected under 35 U.S.C. § 112, first paragraph (written description).

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed November 30, 2004, Appellants filed a Response with arguments and no amendments. An Advisory Action was mailed on June 27, 2005. Thus, all claims remained rejected for the reasons set forth in the Final Office Action and Advisory Action and have not been amended since the Final Office Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter relates to recombinant alphavirus particles comprising an alphavirus replicon (page 15, lines 16-18) and an amino acid mutation in its E2 glycoprotein. The alphavirus replicon comprises a heterologous sequence (page 6, lines 7-13) and the amino acid mutation in the E2 glycoprotein is in the region corresponding to amino acids 158 to 162 (page 5, lines 4-12), numbered relative to wild type SIN E2 glycoprotein (page 37, lines 22-26). Furthermore, the particles are capable of infecting human dendritic cells (page 4, line 20), but are not derived from ATCC # VR 2526 (page 4, lines 20-21).

The recombinant alphavirus particles of the invention may be a Sindbis virus (page 5, line 10), for example in which the amino acid substitution at E2 residue is at residue 160, as compared to wild type Sindbis virus (page 37, lines 22-26). Alternatively, the recombinant alphavirus particles of the invention may be Semliki Forest virus (page 5, line 9), Ross River virus (page 5, line 9) or Venezuelan equine encephalitis virus (page 5, line 10).

VI. GROUNDS OF REJECTION

1. Claims 17, 19 and 21-23 stand rejected under 35 U.S.C. § 112, 1st paragraph as not being adequately described by the specification as filed.

VII. ARGUMENTS

1. The Specification Describes the Claims on Appeal

Claims 17, 19 and 21-23 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly not described by the specification as filed. In support of the rejection, the Advisory Action stated (pages 3-4):

> Applicants only describe one species of recombinant alphavirus that is made by Sindbis (SD) virus mutated at amino acid residue 162[1] of E2 glycoprotein, wherein the recombinant virus vector is capable of infecting human dendritic cells, whereas a regular SD virus or other regular alphavirus is unable to

[1] Appellants note that the exemplified species includes a mutation at position 160 of E2. In any event, for the reasons of record and those detailed below, possession of the claimed subject matter has been established.

> sufficiently infect. Applicants do not have possession of any or all generic recombinant alphavirus vector with mutations at the claimed amino acid residues of 158-162. Applicants have neither conveyed their possession of making such generic mutated alphavirus vectors, nor have [they] shown their reduction to practice for making such claimed generic alphavirus vector at the time the application was filed. Therefore, the rejection under 35 U.S.C. 112, 1st paragraph is maintained.

Simply put, it was alleged that the genus encompassed by the claimed alphavirus particles, having a mutation at one or more of the 5 specified amino acid positions of E2, is not described by the specification as filed.

Appellants submit that there is ample description in the specification regarding alphavirus particles that infect human DCs and which have a mutation in the 5 specified amino acid residues. As such, the written description requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

(a) The Claims Are Drawn to Particular Alphavirus Particles Fully Described By The Specification As Filed

Any written description inquiry must begin with proper claim construction. Here, the claims on appeal are not drawn to any and all recombinant alphavirus particles having any mutation. In fact, the genus encompassed by the claims on appeal is nowhere near as broad as that painted by the Examiner. Not only must the claimed particles infect human dendritic cells, they must have a mutation in one or more of 5 specified amino acids, determined relative to a wild-type Sindbis alphavirus. Moreover, the claimed genus of alphavirus particles specifically excludes ATCC # VR 2526.

When the claims are properly construed, it is plain that they are drawn to the relatively small genus of recombinant alphavirus particles as claimed, namely recombinant alphavirus particles that infect human dendritic cells and include a mutation in at least one of 5 specific amino acid residues in their E2 protein. Thus, Appellants submit that the Examiner has failed to analyze what is actually claimed and, accordingly, improperly asserts that a single representative

species does not adequately describe the claims. In fact, the evidence of record that these claims are more than adequately described by the specification as filed.

It is well-settled law that fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas Cath, Inc. v. Mahurkar*, 935 F.2d 1557, 19 USPQ2d 1111. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976). It is not necessary that the application describe the claimed invention in *ipsis verba*. Rather, all that is required is that the specification reasonably convey possession. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971). Finally, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange*, 209 USPQ 288 (CCPA 1981).

The Patent Office Guidelines are in accord and stress not only proper claim construction prior to analysis, but also indicate that the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099):

> [t]he description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics.

In the pending case, the specification as filed provides more than ample description of all claimed elements, including both the not conventional and the conventional. In particular, that which is new, namely an alphavirus particle that infects human dendritic cells and in which one or more of residues 158-162 of E2 (numbered relative to Sindbis) is(are) mutated is clearly described in the specification as filed (*see,* page 4, lines 19 to 22; page 5, lines 4 to 10 of the specification, emphasis added):

> Within one aspect of the present invention, isolated alphaviruses and recombinant alphavirus particles are provide which infect human dendritic cells, (with the proviso that the alphavirus is not ATCC # VR-2526 or said alphavirus particle is not generated in total from ATCC # VR-2526.
>
> Within certain embodiments of the above, the alphavirus or recombinant alphavirus particle that **has an amino acid substitution in the E2 glycoprotein as compared to wild-type, for example, at residue 158, 159, 160, 161, or, 162.** Within preferred embodiments, the amino acid substitution is at E2 residue 160. Within other embodiments, the alphavirus has an amino acid deletion or insertion in the E2 glycoprotein. **Within further embodiments, the alphavirus is a Semliki Forest virus, a Ross River virus, a Venezuelan equine encephalitis virus, a Sindbis virus, or ATCC No. VR-2643.**

Furthermore, although not required because it was conventional at the time of filing, the specification also clearly describes how Sindbis (the exemplified species) was considered to be the prototype for all alphaviruses, including SFV, VEE and RRV (whose E2 sequences were also known) (*see,* page 1, lines 12-13; page 2, lines 8-15; page 32, lines 6-12 page 21, line 5 to 19 of the specification, emphasis added):

> Alphaviruses comprise a group of genetically, structurally and serologically related arthropod-borne viruses of the *Togaviridae* family. ...
>
> Sindbis virus is the prototype member of the *Alphavirus* genus of the *Togaviridae* family. Its replication strategy is well characterized and serves as a model for other alphaviruses [citation omitted]. The genome of Sindbis virus (like other alphaviruses is an approximately 12 kb single-stranded, positive-sense RNA molecule that is capped and polyadenylated. Genome RNA is contained within a virus-encoded capsid protein shell which is, in turn, surrounded by a

host-derived lipid envelope from which two viral-specific glycoproteins, E1 and E2, protrude as spikes from the virion surface.

In order to demonstrate the viruses of the Alphavirus genus, including those previously characterized as non-lymphotropic or previously shown to infect murine dendritic cells, could be modified or adapted to efficiently infect and propogate in human dendritic cells, **Sindbis virus was chosen as the representative example. Other similar alphaviruses, such as Semliki Forest virus, Venezuelan equine encephalitis virus and Ross River virus, also may be readily substituted by one of skill in the art, using the disclosure provided herein.**

Representative examples of suitable alphaviruses include Aura virus (ATCC VR-368), Bebaru virus (ATCC VR-600, ATCC VR-1240), Cabassou virus (ATCC VR-922), Chikungunya virus (ATCC VR-64, ATCC VR-1241), Eastern equine encephalomyelitis virus (ATCC VR-65, ATCC VR-1242), Fort Morgan virus (ATCC VR-924), Getah virus (ATCC VR-369, ATCC VR-1243), Kyzylagach virus (ATCC VR-927), Mayaro virus (ATCC VR-66, ATCC VR-1277). Middleburg virus (ATCC VR-370), Mucambo virus (ATCC VR-580, ATCC VR-1244), Ndumu virus (ATCC VR-371), Pixuna virus (ATCC VR-372, ATCC VR-1245), Ross River virus (ATCC VR-373, ATCC VR-1246), Semliki Forest virus (ATCC VR-67, ATCC VR-1247), Sindbis virus (ATCC VR-68, ATCC VR-1248; see also CMCC #4640, described below), Tonate virus (ATCC VR-925), Triniti virus (ATCC VR-469), Una virus (ATCC VR-374), Venezuelan equine encephalomyelitis virus (ATCC VR-69, ATCC VR-923, ATCC VR-1250 ATCC VR- 1249, ATCC VR-532), Western equine encephalomyelitis virus (ATCC VR-70, ATCC VR-1251, ATCC VR-622, ATCC VR- 125-1), Whataroa virus (ATCC VR-926), and Y-62-33 virus (ATCC VR-375).

In addition, again although not required because it was conventional at the time of filing, the specification also clearly describes production and use of recombinant alphavirus particles from various alphaviruses (*see,* page 3, line 23 to page 4, line 8; page 20, line 24 to page 21, line 4 of the specification):

Several members of the alphavirus genus are being developed as expression vectors, including, for example, Sindbis virus [citations omitted], Semliki Forest virus [citation omitted] and Venezuelan equine encephalitis [citation omitted]. ... Because the vector replicons do not express the alphavirus structural proteins necessary for packaging into recombinant alphavirus particles, these proteins [E2] must be provided *in trans*.

> A wide variety of alphavirus-based gene delivery vectors may be readily generated using the disclosure provided herein. Representative examples of such vectors include RNA vector replicons, alphavirus vector constructs, and recombinant alphavirus particles. Briefly, sequences encoding wild-type alphaviruses suitable for use in preparing the above described vectors can be readily obtained from naturally occurring sources, or from depositories (*e.g.*, the American Type Culture Collection, Rockville, Maryland).

Simply put, Appellants have demonstrated possession of the claimed invention by clearly describing that which is new -- mutations at residues 158-162 which impart DC-tropism. Furthermore, although not required because it was conventional at the time of filing, the specification as filed also amply describes production of recombinant alphavirus particles and alphavirus sequences that can serve as the source for the alphaviral sequences. Accordingly, one of skill in the art would have known from the specification's teachings and state of the art that Applicants were in possession of the claimed alphavirus particles at the time of filing and the written description requirement is satisfied.

(b) Disclosure Of A Single Species Can Satisfy The Written Description Requirement

Furthermore, the Examiner is inaccurate in asserting that Appellants are limited to claiming only exemplified species -- in this case, DC-tropic molecules derived from the prototypical alphavirus Sindbis and having the specified amino acid mutations in the E2 glycoprotein. It is axiomatic that working examples are never required for description and that satisfaction of the written description requirement is determined by what the specification reasonably conveys to the skilled artisan. Thus, the flexibility and wide applicability of the claimed compositions should not be used as a basis for asserting that they are incompletely described; and any requirement for Appellants to actually exemplify DC-tropic recombinant alphavirus particles derived from alphaviruses other than SIN is both unnecessary for compliance

with written description requirements and would prevent them from claiming what they believe to be their invention.

Indeed, it is well settled that description of a single species can provide an adequate description, even for a broad genus. Thus, disclosure of a recombinant alphavirus particle that infects human dendritic cells and includes a mutation at residue 160 of E2, as numbered relative to wild-type SIN, is sufficient to establish that Appellants were in possession of the claimed subject matter at the time of filing.

In this regard, the PTO guidelines on written description (see, pages 5-6 above) include various Examples that establish that disclosure of a single species can more than adequately describe a genus. These Examples were favorably commented on by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d (Fed. Cir. 2002).

In particular, Example 9, entitled "hybridization" states the following (emphasis added):

> **Specification**: The specification discloses a single cDNA (SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO:1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequences. ... These sequences may or may not be the same as SEQ ID NO:1.
>
> **Claim**: An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.
>
> **Analysis**: A review of the full content of the specification indicates that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO:1 under highly stringent conditions and encodes a protein with a specific function. The art indicates that hybridization techniques using a known DNA as probe under highly stringent conditions were conventional in the art at the time of filing.
>
> The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 and must encode a protein with a specific activity.

The search of the prior art indicates that SEQ ID NO:1 is novel and unobvious.

There is a **single species disclosed** (a molecule consisting of SEQ ID NO:1) that is within the scope of the claimed genus.

Now turning to the **genus analysis**, a person of skill in the art would **not** expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization **conditions set forth in the claim yield structurally similar** DNAs. **Thus, a representative number of species is disclosed, since** highly stringent hybridization **conditions in combination** with the coding function of DNA and **the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention**.

Conclusion: The claimed invention is adequately described.

The written description inquiry for the claims on appeal is highly analogous to that of Example 9. Here, a review of the full content of the specification indicates that the essential feature of the claimed invention is a mutation in one or more of 5 specified amino acids of E2 such that the recombinant alphavirus particle infects human dendritic cells. The art indicates that it was conventional at the time of filing to make recombinant alphavirus particles comprising wild-type E2. Furthermore, the art indicates that mutation techniques were also conventional in the art at the time of filing and, indeed, the structure of E2 following the 5 particular amino acid residues targeted for mutation would be highly predictable. In other words, the specification's clear description of the unconventional elements of the claimed subject matter is more than ample to indicate satisfaction of the written description requirement by evincing possession at the time of filing.

Moreover, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because of the requirement in the claims that only certain identified amino acid residues be mutated and that the particle infect human DCs. Therefore, it would be expected that such mutations would yield structurally similar recombinant alphavirus particles, regardless of the alphavirus from which they are derived or where in

positions corresponding to 158-162 the mutation occurs. Accordingly, a representative number of species is disclosed, since the identification of 5 specific residues targeted for mutation in combination with the function of infecting human dendritic cells and the level of skill and knowledge in the art are adequate to determine that Appellants were in possession of the claimed invention at the time of filing.

Like Example 9, Example 14 of the PTO Guidelines, entitled "product-by-function," also illustrates a fact pattern that is highly instructive in the pending case (Example 14, emphasis added):

> **Claim**:
> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→ B.
>
> **Analysis**:
> ... The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. ....
>
> **There is actual reduction to practice of a single disclosed species**. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. **The single species disclosed is representative** of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion**: The disclosure meets the requirements of 35 U.S.C. § 112, first paragraph as providing adequate written description for the claimed invention.

As with Example 9, the claim, analysis and conclusion set forth in PTO Example 14 are also directly relevant and analogous to the written description analysis in the pending case. In particular, the pending claims are analogous to the "product by function" claim presented in PTO Example 14 in that they all recite a reference structure (wild-type E2), the particular mutations (95% identity in Example 14 and residues 158-162 in the claims on appeal) and include a function limitation (catalytic activity in PTO Example 14 and infection of human dendritic cells in the claims on appeal).

Furthermore, as noted above, procedures for making recombinant alphavirus particles were utterly conventional in the art at the time of filing and described in the pending application. Also conventional in the art and described in the specification are methods of mutating particular amino acids and methods of determining whether these particles infect human dendritic cells.

Certainly, actual reduction to practice of a single disclosed species is more than sufficient to satisfy the written description requirement in the case at hand because, as in PTO Examples 9 and 14, sequences falling within the claimed genus must have the recited structure and function. Indeed, the genus encompassed by the claims on appeal is even narrower than that of Examples 9 and 14 inasmuch as stringent hybridization conditions and 95% identity include many more possible species than the claims on appeal, in which, at most, 5 amino acid residues are substituted.

Therefore, as in PTO Examples 9 and 14, the genus encompassed by claims 17, 19 and 21-23 is more than adequately described by the specification as filed. Put another way, a person having ordinary skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus, and it is clear that, as concluded in PTO Examples 9 and 14, the written description of these claims in the pending case provides adequate written description for the claimed subject matter.

There is absolutely no requirement that Appellants demonstrate that each and every substitution at positions 158-162 produce a recombinant alphavirus particle that actually infects human dendritic cells. Nor is there any requirement that Applicants exemplify (or reduce to

practice) every alphavirus E2 protein falling within the scope of the claims in order to adequately describe the claimed recombinant alphavirus particles. Rather, the test is whether the specification contains sufficient disclosure regarding structural and functional characteristics of the claimed particles to satisfy the written description requirement.

For the reasons of record, reiterated herein, the specification as filed, in view of the state of the art, more than adequately describes and details structure and function of the claimed expression cassettes.

(c) Declaratory Evidence Of Record Has Not Been Properly Considered

In addition to ignoring the clear teachings of the specification, the Office has not considered declaratory evidence that is relevant to a written description inquiry.

The Office must consider evidence provided by the applicant that the specification as filed indicates that the applicant was in possession of the claimed invention at the time of filing. *See, e.g., In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. Indeed, in *In re Alton,* 37 USPQ2d 1578 (CAFC 1996), the Court of Appeals for the Federal Circuit held that it was error for the Examiner to dismiss with conclusory statements not only factual statements but also statements of opinion presented in Declarations made by qualified persons of ordinary skill in the art. The court commented that they were "aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner. [citation omitted]." *In re Alton,* 37 USPQ2d 1578 at 1583 n10.

In the present case, the Examiner has not considered how the Declaratory evidence of record is relevant to a written description inquiry. In fact, Dr. Polo's Declaration is relevant to both enablement and written description, establishing, what was conventional (routine) at the time of filing and, as such, need not be described in detail in the specification. Specifically, Dr. Polo notes the following facts and arrives at his conclusions using these facts.

First, Dr. Polo establishes that, at the time of filing, both the nucleotide and the amino acid sequence of E2 proteins of many alphaviruses were known and published. *See,* paragraph 8 of Evidence Appendix attached hereto; citing page 21 of the specification). Moreover, Dr. Polo also establishes that the amino acid sequence of any alphavirus that was not known could be easily obtained using conventional methods. *Id.*

Second, the specification describes how to mutate one or more of the amino acid residues corresponding to residues 158-162 of SIN E2 and indicates that making such mutations was conventional at the time of filing. *See,* paragraph 9 of Evidence Appendix attached hereto, citing page 34 of the specification.

Third, this declaration demonstrates that producing recombinant alphavirus particles was conventional at the time the specification as filed. *See,* paragraph 10 of Evidence Appendix attached hereto, citing page 34 of the specification.

Fourth, the specification describes how to test for alphavirus particles having a mutation in the recited 158-162 residues for their ability to infect human dendritic cells. *See,* paragraph 11 of Evidence Appendix attached hereto, citing pages 40 and 42 of the specification.

On the basis of the foregoing, factual statements, Dr. Polo concluded that a skilled worker could have readily designed, made, tested and used a recombinant alphavirus particle falling within the scope of the claims:

> 14. Thus, it is my opinion that making and using recombinant alphaviruses of the claimed invention was a predictable art. I have no doubt that as of April 1999 a person of skill in the art was capable of making the alphavirus mutants and testing them for the ability to infect human dendritic cells. ...
>
> 15. In view of the foregoing facts regarding the routine nature of experimentation required to make and use the claimed recombinant alphaviruses, the extensive direction provided by the specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in April 1999, a skilled worker to practice the methods as claimed.

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Polo confirms that the specification enables the claims throughout their scope. However, Dr. Polo's declaration is also directly applicable to a written description inquiry in that it clearly demonstrates that Appellants were in possession of the claimed invention at the time of filing. Specifically, Dr. Polo's declaration establishes that Appellants were in possession of that which was new (mutation in residues 158-162 that imparts DC-tropism) at the time of filing. Moreover, although not required, this evidence also demonstrates that that which was not new (alphavirus E2 sequences, making amino acid mutations, making recombinant alphavirus particles) and that what is new (mutation in residues) is extensively described in the specification.

Thus, the evidence of record contradicts the Examiner's assertions that the specification does not provide adequate written description for the claimed subject matter, demonstrating instead of the Appellants were in possession of the claimed subject matter at the time of filing. Accordingly, rejection cannot be sustained and should be withdrawn.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are fully described by the specification as filed throughout their scope. Accordingly, Appellants request that the rejection of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: July 14, 2005

By: 

Dahna S. Pasternak
Registration No. 41,411
Attorney for Appellants

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

CLAIMS INVOLVED IN THE APPEAL

1 to 16. (canceled).

17. (previously presented): A recombinant alphavirus particle comprising

an alphavirus replicon comprising a heterologous sequence; and

an amino acid mutation in its E2 glycoprotein, wherein the mutation in the E2 glycoprotein is in the region corresponding to amino acids 158 - 162, numbered relative to wild-type SIN E2 glycoprotein, and further wherein said particle is capable of infecting human dendritic cells, with the proviso that said recombinant alphavirus particle is not derived from ATCC # VR-2526.

18. (canceled).

19. (previously presented): The recombinant alphavirus particle of claim 17 wherein said alphavirus is a Sindbis virus.

20. (original): The recombinant alphavirus particle according to claim 19 wherein said alphavirus has an amino acid substitution at E2 residue 160, as compared to wild-type Sindbis virus.

21. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Semliki Forest virus.

22. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Ross River virus.

23. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Venezuelan equine encephalitis virus.

24 to 37. (canceled).

EVIDENCE APPENDIX

The evidence appendix includes one document: DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF JOHN M. POLO, PHD.

The document in the evidence appendix was submitted by Applicants in the Amendment mailed on July 25, 2003 (responsive to a non-Final Office Action mailed on January 27, 2003).

The evidence in the following appendix was acknowledged as received and entered in the record by the Examiner in a Final Office Action mailed on September 25, 2003.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: POLO et al.	Examiner: B. Li
	Group Art Unit: 1648
For: COMPOSITIONS AND METHODS FOR GENERATING AN IMMUNE RESPONSE UTILIZING ALPHAVIRUS-BASED VECTOR SYSTEMS	Confirmation No.: 2230
Serial No.: 09/551,977	DECLARATION OF JOHN POLO PURSUANT TO 37 C.F.R. § 1.132
Filed: April 14, 2000	
Atty. Docket No.: PP01593.004 (2300-1593)	

Mail Stop Non-Fee Amendment
P.O. Box 1450
Commissioner for Patents
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF JOHN M. POLO, Ph.D.

Dear Sir:

I, John M. Polo, hereby declare as follows:

1. I received my Ph.D. in Virology from North Carolina State University in 1990. I am currently Director, Vaccine Research at Chiron Corporation in Emeryville, CA and have been at Chiron since 1995. Before joining Chiron, I was a Scientist at Viagene, Inc., in San Diego, CA. A copy of my Curriculum Vitae (Exhibit A) is attached hereto.

2. I am extremely familiar with studies of virology, virus vectors and vaccines, having worked in these disciplines for almost 20 years. I have also co-authored numerous publications and patents in these fields.

3. I have reviewed the pending Patent Application Serial No. 09/551,977 for "COMPOSITIONS AND METHODS FOR GENERATING AN IMMUNE RESPONSE UTILIZING ALPHAVIRUS-BASED VECTOR SYSTEMS" (herein after the "specification") and the currently pending claims. I have also reviewed the Office Action dated January 27, 2003

and the references cited therein including Tucker *et al.*, *J. Virol.* 1997, Vol. 71, pp. 6106-6112 (hereinafter "Tucker") and MacDonald *et al.*, *J. Virol.* 2000, Vol. 74, pp. 914-922 (hereinafter "MacDonald"). Therefore, I am familiar with the issues raised by the Examiner in the Office Action.

4. I understand that the pending claims are directed to recombinant alphavirus particles that are capable of infecting human dendritic cells. In addition, the claimed particles include an amino acid mutation the E2 glycoprotein as compared to the wild-type alphavirus sequence from which the recombinant particles are derived. Specifically, the mutation(s) are found in one or more residues that correspond to amino acids residues numbered 158 to 162 in Sindbis (SIN). The pending claims exclude recombinant alphavirus particles that are derived from ATCC # VR-2526.

5. It is my opinion that, as a technical matter, a skilled worker could have readily made and used the compositions of the pending claims in light of the specification, together with the common general knowledge, tools and methods available as of the effective filing date of April 1999. It is further my opinion that the references cited by the Examiner (Tucker and MacDonald) do not teach or suggest problems with the enablement of the pending claims. I base these opinions on the facts set forth below; however, I call attention to the fact that it was considered routine experimentation at the time of filing to culture human dendritic cells and to introduce specific mutations in amino acid sequences. I also call attention to the fact that the specification provides abundant direction regarding testing the ability of an alphavirus particle to infect human dendritic cells. In drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the direction present in the specification, the state of the field at the time the application was filed, the teachings of the cited references and the level of skill in the art.

6. At the outset, I note that the term "skilled worker" is a worker with a routine level of skill in the fields of molecular biology and virology in April 1999 with a Ph.D. degree and two or more years of post-doctoral training. In view of my training and experience, I am currently, and was in April 1999, such a skilled worker.

7. When the specification was filed, it clearly taught a typical scientist how to make and use recombinant alphavirus particles from a variety of alphavirus species, where the particles are capable of infecting human dendritic cells and contain an amino acid mutation at positions 158-162 (based on SIN numbering) of E2 (relative to the wild-type alphavirus source). Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of the claims and enabled a typical scientist to make and use the invention as set forth in the pending claims. I base this belief on the facts set forth below.

8. First, at the time the specification was filed, both the nucleotide and the amino acid sequence of the E2 proteins of a many alphaviruses were known and published. (See, for example, page 21 and background section of the specification). The amino acid sequences of any alphavirus that was not known could have been easily obtained by standard sequencing techniques using RNA isolated from alphaviruses. It was also known at the time of filing that Sindbis (SIN) was considered the prototype and model for other alphaviruses. (See, *e.g.*, page 2, lines 8-16 of the specification). In view of the teachings of the specification, it would have been routine for the skilled artisan to align and compare nucleotide and amino acid sequences from various alphaviruses and determine which amino acid sequences in any alphavirus corresponded to positions 158-162 of a SIN E2 protein. (See, *e.g.*, page 37 of the specification, describing alignment of SIN strains). Also, in view of the disclosure, a person of skill in the art would surmise that mutants in this region would be much more likely to exhibit DC-tropism. Accordingly, it is my opinion that using the teachings of the specification and state of the art, it would require only routine experimentation for a typical scientist to obtain suitable amino acid sequences from any alphavirus (for example by comparison with sequences disclosed in the specification) and use these alphavirus sequences as a starting point for making the claimed particles.

9. Second, in light of the teachings of the specification, it would have been routine for a typical scientist to mutate one or more of amino acid residues corresponding to residues 158-162 of E2. Methods of making amino acid mutations were well known in the art and described, for instance in Example 1 (particularly page 34) of the specification. Further, the production and testing of a particular mutant at residue 160 is described in the specification. It would also have been routine to determine, by structural and/or functional analyses, which amino

acids corresponding to 158-162 could be mutated to develop DC-tropic particles. In light of the teachings of the specification, I believe that a typical scientist would have known how to make and use alphavirus particles including mutations in the specified region of an alphavirus E2.

10. Third, it would have been routine to produce alphavirus particles having the claimed mutation(s) in residues 158-162 of E2. Methods of generating (packaging) recombinant alphavirus particles, for example, through co-transfection of complementing vector and defective helper (DH) molecules or by introduction of vector into stable packing cell lines, were well known at the time of filing. (See, also, page 23, lines 5 to 23 of the specification). Also well known were methods of performing site-directed mutagenesis that would target one of the residues at positions 158-162. Thus, it is my opinion that it would have been routine for the skilled artisan to make recombinant alphavirus particles having the claimed mutation(s) in positions 158-162 of E2.

11. Fourth, it would have been clear to a typical scientist how to test for the ability of a mutant alphavirus particle falling within the scope of the claims to infect human dendritic cells. (See, *e.g.*, page 42 of the specification). Methods of culturing human dendritic cells were known and described in the specification as filed. (See, *e.g.*, Example 1). Moreover, methods of testing the ability of alphavirus particle to infect these cells are described in detail in the specification and include, but are not limited to, testing FACS analysis, titer analysis, use of reporter molecules, and the like. (See, *e.g.*, page 40; page 42-43). Thus, it is my opinion that a typical scientist could have readily tested any recombinant alphavirus particle containing the claimed mutation, following the teachings of the specification.

12. It is further my opinion that MacDonald and Tucker are not relevant to the claimed recombinant alphavirus particles. Neither reference discloses infection of human dendritic cells with recombinant alphavirus particles, as required by all the pending claims. Furthermore, neither references describes, demonstrates or suggests what effect mutations in the claimed region of 158-162 would have on DC-tropism. In this regard, MacDonald discloses mutations only at positions 76 and 116 of E2, while Tucker discloses mutations at positions 55 or 172 of E2.

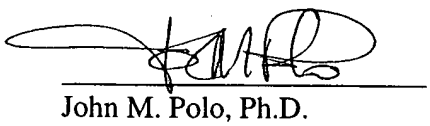
13. In addition, it is my opinion that it would have been clear to the skilled worker at the time the specification was filed that the claims encompassed mutations at one or more of the residues corresponding to residues 158-162 of an alphavirus E2 glycoprotein. It is clear from the specification, for example, on page 5, lines 4-12 that "an" amino acid substitution refers to one or more substitutions in the specified region.

14. Thus, it is my opinion that making and using recombinant alphaviruses of the claimed invention was a predictable art. I have no doubt that as of April, 1999 a person of skill in the art was capable of making the alphavirus mutants and testing them for the ability to infect human dendritic cells. Even if a mutant were inoperable for some reason, e.g., was not capable of infecting human dendritic cells, the skilled worker could have readily modified the mutant according to known techniques. Undue experimentation would not be involved in determining which embodiments were inoperable.

15. In view of the foregoing facts regarding the routine nature of experimentation required to make and use the claimed recombinant alphaviruses, the extensive direction provided by the specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in April 1999, a skilled worker to make and use the compositions as claimed.

16. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

7/22/03
Date



John M. Polo, Ph.D.

John M. Polo

45 Viewpoint Court
Danville, CA 94506
510.923.8140 *office*
925.964.1275 *home*
john_polo@yahoo.com

Professional Experience

Chiron Corporation, Vaccines Research and Development, Emeryville, CA
Director, 2000 - present

Chiron Corporation, Gene Therapy & Vaccines, San Diego/Emeryville, CA
Senior Scientist, 1999 - 2000
Principal Scientist, 1997 - 1999
Research Scientist II, 1995 - 1997

Viagene, Inc., Viral Therapeutics, San Diego, CA
Research Scientist I, 1994 - 1995

University of Southern California, School of Medicine, Los Angeles, CA
Postdoctoral Research Fellow, 1990 - 1994, Preceptor: Dr. Michael Lai

University of North Carolina, School of Medicine, Chapel Hill, NC
Graduate Research Assistant, 1988 - 1990, Preceptor: Dr. Robert Johnston

North Carolina State University, Department of Microbiology, Raleigh, NC
Graduate Research Assistant, 1984 - 1988, Preceptor: Dr. Robert Johnston

Awards and Professional Associations

Registered Patent Agent, U.S. Patent and Trademark Office, #48738
NIH HIV Vaccine Design and Development Contract (6/00-5/05), co-PI
NIH AIDS Vaccine IPCAVD Grant (9/02-8/07), co-Investigator
Howard Hughes Postdoctoral Fellowship (12/90-12/93)
American Society for Virology
American Society for Microbiology
American Society for Gene Therapy
Ad hoc reviewer *Journal of Virology, Virology, Vaccines*

Education

Bachelor of Science, Microbiology - Auburn University, 1984
Doctor of Philosophy, Virology - North Carolina State University, 1990

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2. Gidwitz, S., **J.M. Polo**, N.L. Davis, and R.E. Johnston. 1988. Differences in virion stability among Sindbis virus pathogenesis mutants. *Virus Res.* 10:225-240.

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Patents / Applications

1. U.S. Patent 5,789,245 - Alphavirus structural protein expression cassettes.

2. U.S. Patent 5,814,482 - Eukaryotic layered vector initiation systems.

3. U.S. Patent 5,843,723 - Alphavirus vector constructs.

4. U.S. Patent 6,015,694 - Method for stimulating an immune response utilizing recombinant alphavirus particles.

5. U.S. Patent 6,015,686 - Eukaryotic layered vector initiation systems.

6. U.S. Patent 6,242,259 - Compositions and methods for packaging of alphavirus vectors.

7. U.S. Patent 6,329,201 - Compositions and methods for packaging of alphavirus vectors.

8. U.S. Patent 6,342,372 - Eukaryotic layered vector initiation systems for production of recombinant proteins.

9. U.S. Patent 6,376,236 - Recombinant alphavirus particles.

10. U.S. Patent 6,391,632 - Recombinant alphavirus-based vectors with reduced inhibition of cellular macromolecular synthesis.

11. U.S. Patent 6,426,196 - Alphavirus structural protein expression cassettes.

12. U.S. Patent 6,451,592 - Recombinant alphavirus-based vectors with reduced inhibition of cellular macromolecular synthesis.

13. U.S. Patent 6,458,560 - Recombinant alphavirus-based vectors with reduced inhibition of cellular macromolecular synthesis.

14. WO 96/21416, Methods and compositions for treatment of solid tumors in vivo, *Pending.*

15. WO 00/61770, Enhancement of the immune response for vaccine and gene therapy applications, *Pending.*

16. WO 00/61772, Compositions and methods for generating an immune response utilizing alphavirus-based vector systems, *Pending.*

17. WO 01/81553, Alphavirus-based vectors for persistent infection, *Pending.*

18. WO 01/92552, Methods for the purification of alphavirus replicon particles, *Pending.*

19. WO 02/26209, Microparticles for delivery of heterologous nucleic acids, *Pending.*

20. WO 02/80982, Nucleic acid mucosal immunization, *Pending.*

21. WO 02/99035, Alphavirus replicon particle chimeras, *Pending.*

RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Brief on Appeal and pursuant to 37 C.F.R. § 41.37(c)(i) and (c)(x), Appellants are not aware of any related appeals or interferences which may be related to, directly affect, be directly affected by, or have any bearing on the Board's decision in the pending appeal. Accordingly, no documents are submitted with this Appendix.